REMARKS

The present Amendment and Request for Continued Examination is being submitted in response to the Office Action mailed December 17, 2008.

On pages 4-7 of the Office Action the Examiner rejected claims 30-54 under 35 U.S.C. § 103(a) as being unpatentable over, Mehta et al., United States Patent No. 5,837,284 ("Mehta") in view of Mulye, United States Patent No. 6,475,493 ("Mulye") and Beiman et al., United States Patent No., 6,312,728 (Beiman).

Reconsideration is requested.

Claims 30-54 have been cancelled and new claims 55-78 have been added to the present application. The invention recited in the currently pending claims is a controlled release methylphenidate tablet that comprises two primary elements: 1) an immediate release methylphenidate coating and 2) a controlled release methylphenidate tablet core. The controlled release methylphenidate tablet core comprises a compressed mixture of methylphenidate and a hydrogel polymer and an enteric coating around the compressed mixture. This unique dosage form is further required to exhibit two distinct methylphenidate *in vivo* plasma peaks, or a step profile, when the tablet is administered to humans. In addition, the claimed tablet must exhibit a controlled release of the methylphenidate when tested in a pH 7.5 media and be similar to the *in vitro* curve shown in Figures 4-6 of the present application. The release profiles in Figures 4-6 distinctly show a step release curve wherein an immediate release portion of methylphenidate is released followed by a more gradual and slower release over time of the methylphenidate. This curve is shown in Figures 4-6 and has been incorporated into new independent claims 55, 62 and 71. The remaining elements of new claims 55-78 are essentially the same as the elements recited in claims 30-54 that

were previously pending in the present application. No new matter has been added.

Applicants respectfully submit the presently claimed formulation is patentable over the references of record because none of the references either alone or combined disclose or suggest a methylphenidate tablet that employs a compressed admixture of methylphenidate and a hydrogel polymer which is subsequently coated with an enteric polymer to provide controlled release of the methylphenidate over an extended period of time when tested in high pH environments. Additionally, the cited prior art does not disclose the *in vitro* step profile recited in the new claims. This step profile when used with methylphenidate has been found to be effective in treatment of ADD and/or ADHD. The present application specifically teaches:

> Numerous sustained release formulations of methylphenidate which provide for a slow release of the medication over a predetermined period of time have been developed … However, when methylphenidate is delivered at a steady state over a sustained period of time, acute tolerance often develops. The undesirable clinical effects of steady state sustained release formulations are overcome by multiple dosing whereby the intensity of the therapeutic effects of the methylphenidate can be maintained.

See paragraph 0006 of US 2004/0156896 (U.S. publication of the present application, hereinafter "the '896 publication").

Unfortunately, it has been shown that the known sustained release dosage forms did not provide the needed therapy:

> Sustained release formulations of methylphenidate have been developed, which provide for the slow release of the drug over the course of the day. However it has been observed that peak plasma concentrations of the drug are lower when sustained release formulations are used. Studies have shown that sustained release formulations of methylphenidate have been shown to have lower efficacy than conventional dosage forms.

See paragraph 0009 of the '896 publication.

The present inventors have sought to overcome the deficiencies of the known prior art by

developing a once a day controlled release dosage form that mimicked the release profile of the multiple dosing regimen.

> To overcome the previously mentioned problems with sustained delivery of methylphenidate, the present invention provides the needed delivery system whereby the drug can be administered in a single dose and provide the needed delivery rate so that tolerance to its effects will not develop.

See paragraph 0011 of the '896 publication.

Applicants submit that the cited prior art fails to teach a single controlled release dosage form that contains an immediate release methylphenidate coating and a controlled release methylphenidate tablet core containing a hydrogel polymer that is coated with an enteric polymer, which provides the necessary *in vitro* release profile as shown in Figures 4-6 for successfully treating patients with ADD and/or ADHD.

The release profiles provided by the claimed tablets are not simple modifications or optimizations of known release profiles, but specific release parameters designed for a specific drug, to treat a specific condition. Therefore, combining non-analogous art using the present application as a template does not render obvious the claims of the present application.

Furthermore, the use of a once a day dosing regimen also increases patient compliance and alleviates the problems due to theft of methylphenidate tablets. Theft of methylphenidate tablets is a serious problem due to the known recreations uses of methylphenidate.

Additionally, Applicants submit that the present claims are patentable over the cited references either alone or combined because the cited references fail to disclose or suggest the use of a mixture of a hydrogel polymer and methylphenidate in the core of a controlled release tablet. As indicated above, the present claims all require a compressed core comprising a mixture of methylphenidate and a hydrogel polymer wherein the compressed mixture is coated with an enteric

polymer.

The Mehta reference discloses oral methylphenidate dosage forms that employ immediate release pellets and controlled release pellets. Applicants gratefully acknowledge the Examiner's prior indication that Mehta fails to disclose the use of an enteric polymer. Applicants also respectfully submit that Mehta fails to disclose the use of a compressed admixture of methylphenidate and a hydrogel polymer to control the release of the methylphenidate from the core as required by the pending claims.

On pages 4-5 of the Office Action the Examiner points to Mehta et al. as teaching the compressed core containing a hydrogel polymer and methylphenidate. The Office Action recites that Mehta teaches a dosage form containing methylphenidate and 10 percent of hydroxypropyl methylcellulose (HPMC). The Examiner further states on page 2 of the Office Action that this recitation of HPMC renders obvious the Applicants' use of a hydrogel polymer, because one of the hydrogel polymers recited in Applicants' dependent claims is HPMC. Applicants submit that the Examiner is in error based on this review of Mehta. A detailed review of Example 1 of Mehta shows that Example 1 teaches use of "HPMC E-6 from Dow Chemicals, Midland, Mich". HPMC E-6 is not a "hydrogel polymer". In contrast, HPMC E-6 is a very low viscosity polymer. See Rowe et al., *Handbook of Pharmaceutical Excipients*, p. 297-300 (4th Ed. 2003), which indicates that HPMC E-6 has a viscosity in the range of 5-7 mPa's (Exhibit A, submitted with the Reply dated August 18, 2008).

The specification of the present application specifically teaches the use of hydrogel polymers such as Methocel K-100M Premium (See Examples 1-4 of the present specification). This hydrogel polymer has a very high viscosity, in the range of 80,000 to 120,000 mPa's as can

be seen at page 298 of Exhibit A submitted with the Amendment dated August 18, 2008. A high viscosity is required for a polymer to be considered a hydrogel polymer. Further the hydrogel polymer assists in the production of the claimed release characteristics of the present invention as shown in Figures 4-6.

Therefore, Mehta et al. does not teach a controlled release tablet core containing methylphenidate and a hydrogel polymer, but the combination of methylphenidate and a low viscosity polymer.

Applicants note that on page 2 of the Office Action, the Examiner states that because Applicants' dependent claims recite HPMC as a possible hydrogel polymer, that the use of any grade of HPMC renders obvious the use of a hydrogel polymer as recited in the claims of the present application. Applicants submit that this reasoning is incorrect. A hydrogel polymer is known in the art as a material that gels or swells in the presence of water. The gelling and/or swelling controls the release of a drug from the resulting matrix by diffusion, erosion, or a combination of diffusion and erosion. The independent claims of the present invention limit the polymer used in the core to a hydrogel polymer. Several types of polymers are then listed in the dependent claims as examples of materials that may be used as hydrogel polymers. However, the claim limitation is still to hydrogel polymers, and therefore, any grade of material listed must be a hydrogel polymer, i.e., a polymer that gels and swells to control the release of the drug. Therefore grades of HPMC that are not hydrogel polymers, or which do not gel or swell to control the release of drug, i.e., actually allow the immediate release of drug, are not encompassed within the scope of the present claims. Therefore, the Examiner's reasoning that the Mehta patent's uses of low viscosity HPMC renders obvious the use of hydrogel polymers in

the present application is incorrect, as a matter of fact and a matter of law. *See* Application of Ehrreich, 590 F.2d 902. 906-907 (CCPA 1979).

The Examiner references Mulye and Beiman to alleviate the deficiencies of Mehta. However, Applicants submit that Mulye and Beiman do not fill the gaps left by Mehta, and more particularity teach away from the claims of the present invention.

The addition of the Mulye reference to the Mehta reference fails to suggest to an individual of ordinary skill the controlled release methylphenidate tablet recited in the currently pending claims. In fact, the Mulye reference would lead an individual of ordinary skill away from the presently claimed invention. The Mulye reference discloses multi-particulate dosage forms, not compressed tablet dosage forms, wherein the release of the drug is controlled by the coating and not a combination of a coating and a hydrogel under the coating. Furthermore, Mulye does not disclose a dosage form that produces the required in vitro step profile shown in Figures 4-6 of the present application. Therefore, Mulye, alone or in combination with the other cited art, does not render obvious the claims of the present invention which are directed towards compressed, non-multi-particulate dosage forms that provide a specific step profile necessary to treat ADD or ADHD.

Next the Examiner references Beiman et al. to alleviate the remaining deficiencies of Mehta and Mulye. The addition of the Beiman reference to the teachings of the Mehta and Mulye references also fails to overcome the deficiencies of the Mehta/Mulye proposed combination. First, the Beiman reference also teaches multi-particulate dosage forms, and it fails to mention methylphenidate. It is respectfully submitted that an individual of ordinary skill would not look to the Beiman reference for guidance on preparing controlled release methylphenidate tablets due to the lack of a methylphenidate dosage from disclosure. Furthermore, the present claims are directed

towards tablets that provide a specific *in vitro* release profile which has been demonstrated to be effective at treating ADD and/or ADHD. None of these teachings are contained or suggested in Beiman, and therefore Beiman does close the gaps left by Mehta and/or Mulye.

Applicants submit that combining the disclosures in Mehta, Mulye and Beiman only teaches dosage forms using low viscosity polymers in multi-particulate formulations, not compressed tablet formulations containing a hydrogel polymer that gels and swells to control the release of the drug. Further, none of the references teach or suggest the *in vitro* curves of Figures 4-6 of the present application. The release profiles provided by the claimed tablets are not simple modifications or optimizations of known release profiles, but specific release parameters designed for a specific drug, to treat a specific condition. Therefore, combining non-analogous art using the present application as a template does not render obvious the claims of the present application.

Because the cited prior art references do not disclose or suggest the combination of methylphenidate and a hydrogel polymer in the core of a controlled release tablet coated with an enteric polymer, and surrounded by an immediate release layer of methylphenidate, and wherein the tablet provides the claimed *in vitro* step release profiles, it is requested that the above 103(a) rejection be withdrawn.

Based upon the above remarks, new claims and Request for Continued Examination, Applicants respectfully submit that new claims 55-78 are allowable over the prior art and that the present application is in proper form for allowance. Favorable consideration and early allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

/Nicholas P. Chiara/

Nicholas P. Chiara
Reg. No. 52,737

MAILING ADDRESS:
HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, NY 10036-2601
(212) 302-8989